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Terezine E, bioactive prenylated tryptophan analogue from an endophyte of *Centaurea stoebe*

Randa Abdou^{1,2}, Samah Shabana³ and Mostafa E Rateb^{4,5,*}

¹ Department of Pharmacognosy, Faculty of Pharmacy, Helwan University, Egypt,

² Department of Pharmacognosy, faculty of Pharmacy, Umm Alqura University, Kingdom of Saudi Arabia,

³ Department of Pharmacognosy, Faculty of Pharmacy, Misr University for Science & Technology (MUST), Egypt,

⁴ Department of Pharmacognosy, Faculty of Pharmacy, Beni-Suef University, Egypt,

⁵ School of Science & Sport, University of the West of Scotland, United Kingdom.

Correspondence: mostafa.rateb@uws.ac.uk, Tel: +44(0)1418483072.

Abstract:

Fungal endophytes are considered promising sources of new bioactive natural products. In this study, a *Mucor* sp. has been isolated as an endophyte from the medicinal plant *Centaurea stoebe*. Through bioactivity-guided fractionation, the isolation of the new bioactive terezine E in addition to the previously reported 14-hydroxyterezine D was carried out. The isolated compounds were fully characterised by HRESIMS and 1D and 2D NMR analyses. Both compounds exhibited potent antiproliferative activity against K-562 and HUVEC cell lines and antifungal efficacy against the tested fungal strains.

Keywords: Terezine E, endophyte, cytotoxic, antimicrobial.

1. Introduction

Medicinal Plants have functioned as a source of pharmaceutical bioactive compounds against several forms of illnesses for decades. Unluckily, in current years, microorganisms associated with plants instead have proved to produce bioactive compounds with potent pharmacological and therapeutic activities (Kusari et al. 2013). A variety of microscopic species are known to be endophytes, inhabiting inter and intracellular spaces of tissues of advanced plants without causing actual damage on the plants in which they live. Frequently they have been recognised to be rich sources of bioactive natural products (Li et al. 2008; Molina et al. 2012).

Recently, endophytic fungi are of biotechnological attention because of their prospective as a source of novel secondary metabolites that has been recognized useful for new drug discovery (Kusari et al. 2013). It has been reported that plant endophytic fungi showed antifungal and antibacterial activities (Bhardwaj et al. 2015). Several pharmacological activities have been proven for endophytic fungal metabolites such as the anticancer cajanol (Zhao et al. 2013), cytotoxic radicicol (Turbyville et al. 2006), podophyllotoxin and kaempferol (Huang et al. 2014), anti-inflammatory ergoflavin (Deshmukh et al. 2009), antioxidant lectin (Sadananda et al. 2014), insecticidal heptelidic acid (Zhang et al. 2014), antimycotics steroid 22-triene-3 β -ol (Metwaly et al. 2014), and immunosuppressive sydoxanthone A and B (Song et al. 2013). The choice of a suitable host plant is crucial for the process of searching for new bioactive natural compounds. It is therefore important to follow reasonable strategies that provide good opportunities to isolate productive endophytes. Since the number of plant species in the world is so large, creative strategies must be used to narrow the search for bioactive endophytes (Kusari et al. 2013). Strobel, et al had summarized the potential plant selection strategies as follows: (i) plants from unique environments develop

novel survival strategies, (ii) plants having specific biological activities are a promising source for study, (iii) plants that have an unusual longevity are mostly associated with endophytes with active natural products, and (iv) plants growing in areas of great biodiversity may harbor endophytes with great biodiversity (Strobel et al. 2004).

Centaurea stoebe (spotted knapweed) is a highly invasive plant in North America upon which several studies have been conducted for more than four decades to find suitable biological control that suppresses its widespread growth (Carson et al. 2014). It is considered as a noxious weed for which resistance against auxinic herbicides (Mangin et al. 2016) as well as drought tolerance have been reported (Mraz et al. 2014).

Several biological activities have been reported for *Centaurea* spp. such as cytotoxic and apoptotic effects of the aqueous extract of Croatian endemic *C. ragusina* on human bladder (T24) and human glioblastoma (A1235) cancer cell lines (Radan et al. 2017), as well as antibacterial activity of different extracts of *C. cyanus* growing wild in Kosovo (Haziri et al. 2017). The anticancer activity of extracts from *Centaurea* species has been furthermore confirmed by a study conducted on the Turkish endemic plant *C. drabifolia* which revealed antiproliferative activity against leukemia cells (Formisano et al. 2017). Previous studies also reported anti-inflammatory activities of *C. sadleriana* (Csupor et al. 2013) and more recently antiphytoviral activity against Tomato bushy stunt virus for phenolic compounds isolated from *C. rupestris* (Curkovic-Perica et al. 2014).

Several phytochemical studies conducted on *Centaurea* species state a wide metabolic profile for the investigated plant extracts through isolation and identification of unusual sesquiterpene lactones (athoin, 14-O-acetylathoin) from *C. athoa* (Demir et al. 2016), a sesquiterpene lactone (cnicin) and several flavonoids from extracts of *C. tomorosii*, *C. soskai* and *C. galicicae* (Tesevic et al. 2014), two lignans; matairesinol and arctiin and two indole alkaloids; N-(*p*-coumaroyl) serotonin and moschamine from seeds of *C. vlachorum* growing

in Albania (Hodaj et al. 2016). New cytotoxic guaianolides cenegyptins A and B were also reported from *C. aegyptiaca* (Sary et al. 2016). In addition, several essential oils have been detected in extracts of *C. formanekii* and *C. orphanidea* (Ben Jemia et al. 2012), as well as polysaccharides and polyphenols from *C. cyanus* (Pirvu et al. 2015).

Taking the previously reported findings in consideration, it was found that the invasive medicinal plant *Centaurea stoebe* that inhabits areas of great biodiversity and has different associated biological activities (Erik et al. 2012) and a wide secondary metabolic profile encouraged us to screen it as a promising source of endophytes.

Screening the fungal community associated with *C. stoebe*, the endophyte *Mucor* sp. was isolated and its fermentation led to the isolation of the antifungal hydroxymellein, an antimalarial diketopiperazine in addition to the antibacterial and antiproliferative compound epicoccin A (Abdou 2014). Later, the bio-guided fractionation of another endophyte associated with *C. stoebe*, *Trichoderma* sp. led to the isolation of α -viridin, β -viridin and adenosyl 9 α -D-arabinofuranoside which showed antifungal as well as cytotoxic and antiproliferative effects against HUVEC, K-562 and Hela cancer cell lines (Abdou and Abduhady 2015).

Bio-guided screening of the endophyte in different culture media indicated its promising biological effects (Abdou 2014). In the current study, large scale fermentation and bio-guided fractionation has led to the isolation of the new bioactive terezine E in addition to 14-hydroxyterezine D. Both compounds exhibited antiproliferative and cytotoxic activities against HUVEC, K-562 and HeLa cancer cell lines.

2. Results and Discussion:

The extract of the endophyte cultivated in medium M5 revealed potent cytotoxicity against HeLa cell lines and strong cytostatic effect against HUVEC and K-562 cell lines. In addition, the extract exerted antimicrobial activity against several bacterial and fungal strains. Bio-guided screening of this extract led to the isolation of two metabolites.

Compound **1** was isolated as a pale yellow powder. Analysis of the high-resolution electrospray ionization mass spectrometry (HRESIMS) gave an $[M+H]^+$ ion at m/z 342.1812, indicating the molecular formula of [this compound](#) to be $C_{19}H_{23}N_3O_3$. Its 1H , ^{13}C and multiplicity-edited HSQC NMR spectral data (Table S1) of indicated the presence of two amide groups, two methyl singlets and one doublet, two methylenes and two methines ([Figure 1](#)). The COSY correlations of H-4 through H-6, 1-NH to H-2, and the HMBC correlations of 1-NH to C-7a and C-3, H-2 to C-3a, C-3 and C-1', H-4 to C-3 and C-7a confirmed the presence of indole ring substructure substituted at position 7. The COSY correlations of H₂-1' to H-2', H-5' to H₃-8' and the HMBC correlations of both H-5' and H₃-8' to C-6' and that of H₂-1' and H-2' C-6' and C-3 established the presence of an indolyl alanyl diketopiperazine (DKP) skeleton. The COSY correlation of H₂-8 to H-9 and the HMBC correlations of both H₃-11 and H₃-12 to C-9 and C-10 indicated a prenyl moiety which was attached to the indole ring at position 7 through the HMBC correlations of H₂-8 to C-6, C-7, and C-7a.

Searching the Dictionary of Natural Product ver. 23.1 on DVD and Reaxys online database indicated **1** to be the prenylated tryptophan DKP analogue, 14-hydroxyterezine D which was previously isolated from the fungus *Aspergillus sydowi* that was recovered from a driftwood sample (PFW1) collected from the beach of Baishamen, China (Zhang et al. 2008). Based on the almost identical NMR and optical rotation data with that of terezine D where its absolute configuration was assigned as L-Ala and L-Try (Wang and Gloer 1995), we propose 14-hydroxyterezine D **1** to have the same configuration.

The molecular formula of compound **2** was established as $C_{19}H_{23}N_3O_4$ based on the HRESIMS analysis which gave an $[M+H]^+$ ion at m/z 358.1761 which indicates one oxygen more than [for 14-hydroxyterezine D 1](#). The analysis of 1H , ^{13}C and multiplicity-edited HSQC NMR spectral data (Table S1, [Figure 1](#)) of [this metabolite](#) revealed [its](#) close similarity [14-hydroxyterezine D 1](#) and the COSY and HMBC correlations confirmed the [presence of the](#)

prenyl tryptophan moiety as identified for 14-hydroxyterezine D **1**. The CNOH group in the molecular formula was assigned as an oxime group, which was supported by the HMBC correlation between H2-1' to C-2' (δ_c 153.4), however the HMBC correlation of H2-1' to C-3' (δ_c 163.6) indicated (*E*)-2-(hydroxyimino)propanamide moiety. This was supported by almost identical NMR shift values of the same moiety in luteoride B (Asai et al. 2011). The COSY correlation of H-5' to H₃-8' and the HMBC correlations of H₃-8' to C-5' and C-6' and H-5' to C-6' and C-3' indicated an alanyl moiety. The close similarity of optical rotation data of both metabolites as well as the common biosynthetic origin allowed us to assign the same absolute configuration of 14-hydroxyterezine D for the new secondary metabolite detected. On that basis, we propose this fungal metabolite to be a new natural product for which we give the name Terezine E.

By investigating the antiproliferative and cytotoxic activities of the isolated compounds against HUVEC, K-562 and HeLa cancer cell lines, significant antiproliferative effects were observed for both compounds with 14-hydroxyterezine D **1** exhibiting higher cytostatic effect and terezine E **2** exerting higher cytotoxicity against HeLa cell line.

Both compounds exhibited potent antiproliferative activity against K-562 and HUVEC cell lines (figures S1 and S2) over a wide concentration range. In both assays, the two compounds showed significant antiproliferative activity with 14-hydroxyterezine D **1** revealing a GI₅₀ value of 38.07 $\mu\text{g.mL}^{-1}$ and 65 $\mu\text{g.mL}^{-1}$ and terezine E **2** a GI₅₀ value of 28.02 $\mu\text{g.mL}^{-1}$ and 27.31 $\mu\text{g.mL}^{-1}$ against HUVEC and K-562, respectively. As for the cytotoxic assay against HeLa cancer cell line (figure S3), CC₅₀ values of 34.09 $\mu\text{g.mL}^{-1}$ and 60.43 $\mu\text{g.mL}^{-1}$ were obtained for 14-hydroxyterezine D and terezine E, respectively. These results indicated that the high antiproliferative activity exerted by terezine E **2** is accompanied with low cytotoxic effect.

Furthermore, the antimicrobial activities of the isolated compounds were examined and revealed moderate antifungal effects for both compounds. The antifungal efficacy was tested against *A. terreus* using nystatin as a positive control and methanol as a negative control. **terezine E** exerted slightly higher antifungal activity than **14-hydroxyterezine D** (MIC 43.6 $\mu\text{g.mL}^{-1}$ for **14-hydroxyterezine D** and 39.7 $\mu\text{g.mL}^{-1}$ for **terezine E**) in comparison with nystatin which exerted MIC-value of 15.63 $\mu\text{g.mL}^{-1}$ against the tested strain.

In the past decade, fungal endophytes have been studied as promising and prolific sources of new pharmacologically and therapeutically active natural products (Gimenez et al. 2007). The exact role of such endophytes inhabiting plant cells is unclear. Recently, several hypotheses have been made to explain the role of endophytes in plants and the types of plant endophyte interactions but the exact role of endophytes in plants is yet to be discovered.

3. Experimental:

Endophyte isolation, fermentation and compound purification. From the medicinal plant *Centaurea stoebe* growing in Idaho, USA, an endophytic fungus has been isolated and identified as a *Mucor* sp. based on ITS sequence comparison as described before (Abdou 2014). Large scale fermentation (40 L) was carried out under optimized growth conditions, static culture in medium M5 which consisted of glycerin (20 g/L), glucose (2 g/L), peptone (10 g/L) and sodium chloride (0.5 g/L), followed by extraction with ethyl acetate which yielded an extract with a dry weight of 13 g that gave a final extract of 9 g after defatting with n-hexane. This methanolic extract was exposed to column chromatographic fractionation using hexane: ethyl acetate (9:1) and then polarity was gradually increased till 100 % ethyl acetate. The obtained fractions were spotted and visualized using thin layer chromatography. Bioactivity guided fractionation was performed and revealed cytotoxic as well as antimicrobial activity for fractions F2, F3. Purification was carried out on Sephadex LH-20

followed by preparative column chromatography using reversed phase silica and a solvent mixture of acetonitrile and water. These purifications resulted in the isolation of 1.3 mg of compound 14-hydroxyterezine D **1** and 1.7 mg of compound terazine E **2** by elution with a 60% acetonitrile/water and 70% acetonitrile/water gradient, respectively.

14-Hydroxyterezine D **1**: pale yellow powder; $[\alpha]_D^{22} +9.6$ (c 0.15, MeOH); UV (MeOH) λ_{\max} (log ϵ) 208 (3.9), 265 (3.6) nm; ^1H NMR and ^{13}C NMR data, Table S1; HRESIMS m/z 342.1812 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_3$ 342.1812).

Terezine E **2**: pale yellow powder; $[\alpha]_D^{22} +11.9$ (c 0.18, MeOH); UV (MeOH) λ_{\max} (log ϵ) 208 (4.2), 260 (3.7), 330 (4.1) nm; ^1H NMR (acetone- d_6 , 600 MHz, Table S1) δ : 1.34 (d, CH_3 -8'), 1.71 (s, CH_3 -11), 1.73 (s, CH_3 -12), 3.52 (d, CH_2 -8), 4.01 (dd, CH_2 -1'), 4.48 (q, CH -5'), 5.48 (t, CH -9), 6.86 (d, CH -4), 6.91 (dd, CH -5), 7.13 (s, CH -2), 7.61 (d, CH -6), 8.11 (s, NH -1); ^{13}C NMR (acetone- d_6 , 150 MHz, Table S1) δ : 18.22 (q, CH_3 -8'), 18.24 (q, CH_3 -12), 25.8 (q, CH_3 -11), 19.4 (t, CH_2 -1'), 30.1 (t, CH_2 -8), 48.5 (d, CH -5'), 110.7 (s, C-3), 115.9 (d, CH -6), 118.7 (d, CH -5), 119.7 (d, CH -4), 123.1 (d, CH -9), 124.4 (d, CH -2), 124.8 (s, CH -7), 128.4 (s, C-3a), 133.1 (s, C-7a), 135.8 (s, C-10), 153.4 (s, C-2'), 163.6 (s, C-3'), 174.2 (s, C-6'); HRESIMS m/z 358.1761 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_4$ 358.1761).

4. Conclusions

In conclusion, a *Mucor* sp. has been isolated as an endophyte from *C. stoebe*. Through bioactivity-guided fractionation, the isolation and characterization of the new bioactive terazine E in addition to the previously reported 14-hydroxyterezine D were accomplished. Both compounds exhibited potent antiproliferative activity against K-562 and HUVEC cell lines and strong antifungal efficacy against the tested fungal strains.

Disclosure statement: No potential conflict of interest was reported by the authors.

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Figure captions:

Figure 1. Compounds isolated from *Mucor* sp.